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EXPERIMENTS ON THE SIDE-EFFECTS OF DRUGS

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The need to study drugs in a way which would allow unbiased analysis of their side-effects arose from the fact that some symptoms of motion sickness closely resemble the side-actions of motion sickness remedies (Glaser and Hervey, 1951). Such an investigation, moreover, could be expected to have fundamental implications and indicate new ways in which drugs could be assessed.

MATERIALS AND METHODS

Subjects.—52 Asian medical students and 20 European members of the British Army took part in this investigation. Four medical students and 10 members of the Army were women. The subjects' ages were between 18 and 31 years. There was no self-selection among the medical students, because an entire class volunteered for this experiment, but the Service men and women volunteered following a request sent to certain troops stationed in Singapore, and they were further selected on account of their doing duties from which they could be spared.

Procedure.—Two separate experiments were performed.

In the first experiment the medical students were given single doses of drugs or a dummy at 7-day intervals. They all took, in turn, 1 mg. of *l*-hyoscine hydrobromide, 25 mg. of promethazine hydrochloride (" phenergan "), 25 mg. of diphenhydramine hydrochloride (" benadryl "), and a dummy, but the order of issuing varied, so that each possible sequence was represented in two or three subjects. The drugs and dummy were indistinguishable and contained identical amounts of colouring, flavouring, and lactose excipient. They were labelled and issued according to a code the key to which was not available until after the results had been worked out, and they were handed out in envelopes marked with the date and the subjects' names. This made it possible to keep the subjects in complete ignorance of the number or types of substances involved. The drugs and dummy were always taken at the same time of the day, ½ hour after breakfast, and during the next 3 hours the subjects' activities were controlled and sedentary. One and a half hours and 3 hours after taking the drugs the subjects were given identical forms in which questions were put in such a way that the presence of symptoms sometimes required an affirmative reply and sometimes a negative one and in which answers could be provided by underlining single words. In order to ensure that no symptoms were missed there was an additional question asking the subjects to describe what were, in their opinions, the effects of the substances taken. The subjects were asked not to rely on memory, but to note their symptoms at the time of observation, even if they themselves considered these symptoms imagined or irrelevant, and they were also asked to record their own pulse rates. At the end of 12 hours they filled in a third and less elaborate questionnaire in which they were asked to record their symptoms after the first 3 hours and in which some scope was given to their recollections of how they had felt during the latter 9 hours. In order to acquaint the subjects with the questionnaires and accustom them to the experiment a preliminary trial was staged under identical conditions, except that no substances were issued.

In the second experiment the members of the Services were tested in two batches, one of 8 and one of 12 subjects, and they were given drugs or a dummy three times daily (in the early morning, at noon, and late in the afternoon) for two 6-day periods separated by one day on which there were no experimental procedures. On the first and last day of each 6-day period dummies were given to all subjects. On the second to fifth day of each period the subjects were given hyoscine or promethazine: half the subjects in each batch took hyoscine during the first week and promethazine during the second, while the other half took these drugs in the reverse order. Hyoscine hydrobromide was given in an initial dose of 1 mg. in the morning of the second day, followed by ½ mg. three times daily, so that 2 mg. was given on the first day and 1½ mg. on subsequent days. Promethazine was given in doses of 25 mg. in the morning and afternoon of the second day, followed by 25 mg. each morning; dummies were given to these subjects at times when medication was not required, so that they continued to take a substance at set hours 3 times daily. This schedule made it necessary to keep the drugs and dummy in correctly labelled containers, but the substances were made up as before and they were again issued in envelopes marked with the subject's name, the date, and the time. Questionnaires were completed every noon and evening, and precautions taken were the same as in the other experiment, so that the subjects could not know what they were taking and what responses were expected.

Discussion of Drugs and Dosage.—The drugs given were chosen because they are probably the most effective preventives of motion sickness. Claims have been made in favour of the 8-chloro-theophyllinates of promethazine ("avomine") and of diphenhydramine ("dimenhydrinate," "dramamine"), but there is reason to believe that the effects of these drugs on motion sickness are the same as those of their hydrochlorides which were given in the present experiment. (The evidence has been reviewed by Glaser and Hervey, 1951.)

The single doses given to the medical students were the same as those given in a previous experiment at sea, and the reasons for choosing these amounts have been stated (Glaser and Hervey, 1951). The dose of diphenhydramine was perhaps somewhat small, but by no means excessively small (Hervey, 1952). In the second experiment the subjects were not available for long enough to test more than two drugs, and it was decided to omit diphenhydramine, which is probably less effective as a motion sickness preventive than hyoscine or promethazine (Strickland, Hahn, and Adler, 1950; Glaser and Hervey, 1951), and which may be inconvenient for continued treatment owing to the short duration of its action (Landau, Marriott, and Gay, 1948). The dosage in this experiment was chosen for a number of reasons. Hyoscine has been used as a seasickness remedy in doses of 2 mg. in 24 hours (Glaser, 1952), but it was feared that prolonged treatment would cause cumulative effects. Fifty mg. of promethazine was considered suitable for the first day, but the action of promethazine is so prolonged that cumulative effects seemed likely even with single daily doses (Bain, Broadbent, and Warin, 1949). Moreover, many people adapt themselves to motion after 24 hours, and nearly all after four days. Thus, in the treatment of motion sickness, a reduction of dosage would be desirable after the first day, both on grounds of cumulative effects and of adaptation to motion, while treatment could usually cease after four days.

Statistical Calculations.—The associations between the frequencies of symptoms were worked out by 2×2 tables, applying Yates's correction for continuity and making use of the χ^2 method.

Results

Effects of Single Doses During the First Three Hours.—Owing to various unavoidable causes only 49 students took part in all tests. The results are given in Table I, and statistically significant differences are shown in Table II. No additional infor-

TABLE I

EFFECTS OF SINGLE DOSES. INCIDENCE OF SYMPTOMS DURING THE FIRST 3 HOURS

Symptom	No. of Subjects Showing Symptom				
	No Treatment (Initial Test)	Dummy	Hyoscine 1 mg.	Promethazine 25 mg.	Diphenhydramine 25 mg.
Asleep	—	—	7	4	1
Drowsiness	22	14	41	35	28
Fatigue	22	12	30	35	24
Inability to concentrate	4	5	14	12	6
Excitement	—	—	3	1	—
Headache	5	10	22	15	8
Nausea	3	10	23	15	8
Giddiness	2	2	26	8	5
Blurred vision	—	2	13	4	4
Ringing ears	—	4	4	1	—
Flushing of face	—	1	11	—	2
Dryness of mouth	14	9	46	14	10
Considers drug pleasant	—	3	5	3	3
Considers drug unpleasant	—	4	33	17	11
Total showing any effect	42	29	48	43	35
Total receiving treatment	52	50	50	50	49

TABLE II

STATISTICAL SIGNIFICANCE OF DIFFERENCES GIVEN IN TABLE I

Only significant differences are given ($p<0.05$). Highly significant differences ($p<0.01$) are marked *

Substances Compared	Symptom	χ^2
Hyoscine—promethazine	Giddiness	12·879*
	Blurred vision	4·536
	Dryness of mouth	40·042*
	Drug considered unpleasant	9·000*
Hyoscine—diphenhydramine	Drowsiness	6·111
	Headache	7·711*
	Nausea	8·799*
	Giddiness	18·204*
	Blurred vision	4·353
	Flushing of face	5·660
	Dryness of mouth	48·753*
	Drug considered unpleasant	17·287*
	Total showing effect	9·288*
Hyoscine—dummy	Drowsiness	27·313*
	Fatigue	11·864*
	Inability to concentrate	4·159
	Headache	5·561
	Nausea	6·605
	Giddiness	26·243*
	Blurred vision	7·951*
	Flushing of face	7·671*
	Dryness of mouth	52·364*
	Drug considered unpleasant	33·633*
	Total showing effect	18·295*
Promethazine—dummy	Drowsiness	16·006*
	Fatigue	19·430*
	Drug considered unpleasant	8·681*
	Total showing effect	8·383*
Diphenhydramine—dummy	Drowsiness	7·453*
	Fatigue	5·637

mation could be obtained by a separate study of the questionnaires completed after one and a half and after three hours (see below), and Table I gives the incidence of symptoms during the first three hours, irrespective of the fact whether a subject reported any particular symptom once or twice during that time.

Drowsiness and fatigue were about equally frequent after hyoscine and promethazine, and significantly more frequent after any drug than after the dummy. Apart from these symptoms, however, hyoscine caused the most side-effects. Thus, after taking hyoscine, over 90% of the subjects had dry mouths, about half the subjects felt giddy, and about a quarter of the subjects complained of blurred vision or flushing of the face, and all these symptoms were significantly less frequent after taking any of the other substances. Moreover, hyoscine was considered unpleasant by a significantly larger number of subjects than any other substance. Inability to concentrate was about equally frequent after hyoscine and promethazine; the difference between hyoscine and the dummy, however, was significant, while the difference between promethazine and the dummy was not statistically significant.

The only apparent discrepancy between questionnaires filled in after one and a half hours and those completed after three hours was that drowsiness and fatigue were more frequent three hours than one and a half hours after taking promethazine, but it was found that this difference was not statistically significant ($\chi^2=3.248$; $p>0.05$).

It is interesting that symptoms were not confined to those included in the questionnaires. Thus, a question was asked about excitement, but only four positive replies were received, three of which were recorded after hyoscine, the only substance likely to cause excitement. No question was asked about flushing of the face, but this symptom was recorded 14 times, 11 of which were after hyoscine.

The average pulse rate was 75 after hyoscine and 80 after the other substances. The difference between hyoscine and the dummy was statistically significant ($t=2.305$; $p<0.05$). On the preliminary day when no drugs were given the average pulse rate was 82.

Table I and Fig. 1 show that symptoms were frequent during the initial test in which no drugs were given. Indeed, significantly more subjects had symptoms on that day than later when they were given dummies ($\chi^2=5.217$; $p<0.05$). When drugs were given, the percentage of subjects who had any symptoms, whatever the treatment, gradually diminished, but there was a sharp rise on the last day (Fig. 1), and significantly more subjects had symptoms on that day than the previous one ($\chi^2=5.742$; $p<0.05$). This does not invalidate the results, because the order of issuing was randomized and an equal number of subjects took each drug on each day, but it has implications which will be discussed below.

Late Effects of Single Doses.—The results are given in Table III, and statistically significant differences are shown in Table IV. Drowsiness was significantly more frequent after promethazine than after any other substance, while dryness of the mouth was significantly more frequent after hyoscine than after the other substances. Giddiness was also the most frequent after hyoscine, but only the difference between hyoscine and the

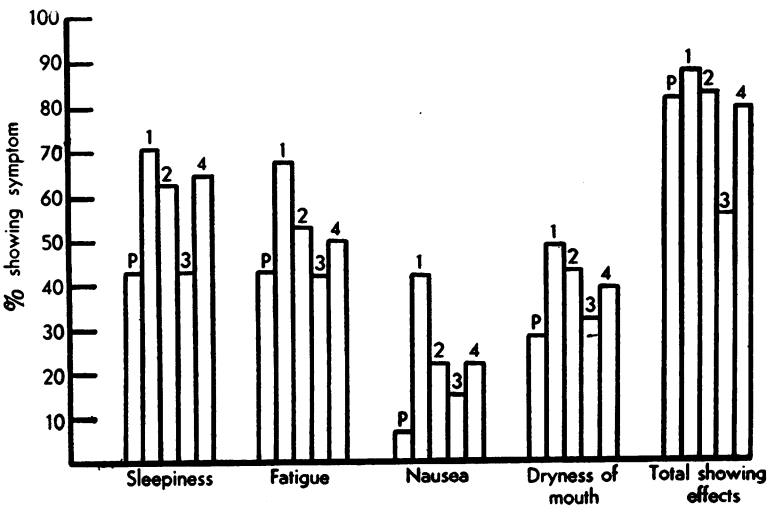

FIG. 1.—Day-to-day incidence of main symptoms during the first 3 hours after taking drugs and dummy. Calculated from all effects recorded on any one day, whatever the treatment. P=preliminary test when no substances were given. Numbers 1–4 indicate successive days when drugs and a dummy were given to similar numbers of subjects.

TABLE III

EFFECTS OF SINGLE DOSES. INCIDENCE OF SYMPTOMS AFTER THE FIRST 3 HOURS

Symptom	No. of Subjects Showing Symptom			
	Dummy	Hyoscine 1 mg.	Promethazine 25 mg.	Diphenhydramine 25 mg.
Drowsiness	3	20	32	8
Inability to concentrate	—	2	5	1
Headache	2	9	9	2
Nausea	—	3	1	1
Giddiness	1	10	4	3
Blurred vision	—	1	1	1
Flushing of face	—	3	1	—
Dryness of mouth	4	20	3	2
Total showing any effect	6	35	32	14
Total receiving treatment	50	50	50	49

TABLE IV

STATISTICAL SIGNIFICANCE OF DIFFERENCES GIVEN IN TABLE III

Only significant differences are given ($p<0.05$). Highly significant differences ($p<0.01$) are marked *

Substances Compared	Symptom	χ^2
Hyoscine—promethazine	Drowsiness	4·848
	Dryness of mouth	14·457*
Hyoscine—diphenhydramine	Drowsiness	5·720
	Dryness of mouth	16·453*
	Total showing effect	15·375*
Hyoscine—dummy	Drowsiness	14·455*
	Giddiness	6·537
	Dryness of mouth	12·333*
	Total showing effect	32·410*
Promethazine—diphenhydramine	Drowsiness	21·420*
	Total showing effect	11·104*
Promethazine—dummy	Drowsiness	34·462*
	Total showing effect	26·528*

dummy was significant. Nine subjects each had headaches after promethazine and hyoscine, and the differences between these and the other substances just failed to be significant ($\chi^2=3.547$ and 3.682 ; $p>0.05$).

The only apparent difference between diphenhydramine and the dummy was a slightly higher incidence of drowsiness after the former, but it was not statistically significant, and this suggests that the effects of diphenhydramine had mostly disappeared after the first three hours.

Effects of Continued Treatment.—Only 17 out of 20 subjects completed the experiment in which drugs were taken repeatedly for four days. One woman withdrew on the first day when she had taken nothing but dummies, another after taking promethazine for one day, and one man after a single dose of hyoscine hydrobromide. The results obtained from the other 17 subjects are given in Table V. Statistical calculations are given in Table VI. Although two questionnaires were completed by each subject on each day there was no significant difference between the answers, and for this reason symptoms noted on each day are shown as a single entry whether they were recorded by one subject once or twice in the same day. On the first day of this experiment when only dummies were given, 12 subjects (70%) had symptoms, and the results generally conformed with those obtained in the other experiment when no substances were given (Table I). The first day of the second six-day period was taken as a control day, because only dummies were given on this day and there had been no medication for two days beforehand.

TABLE V

EFFECTS OF CONTINUED TREATMENT

(17 subjects receiving each treatment)

Symptom	No. of Subjects Showing Symptom								
	Control Day—Dummies Only*	Hyoscine				Promethazine			
		Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
Drowsiness	3	9	9	8	5	10	5	3	3
Inability to concentrate	—	3	1	1	1	—	—	1	—
Excitement	1	2	—	1	—	1	—	1	—
Headache	4	7	4	5	1	5	4	3	2
Nausea	1	4	1	2	3	1	—	—	—
Blurred vision	2	4	5	5	7	2	—	—	—
Flushing of face	2	3	3	7	2	1	2	1	—
Dryness of mouth	3	12	9	5	6	3	1	2	2
Giddiness	—	7	3	2	—	2	1	—	1
Total showing effect	4	13	13	12	11	12	6	6	5

* See text.

TABLE VI

STATISTICAL SIGNIFICANCE OF DIFFERENCES GIVEN IN TABLE V

Only significant differences are given ($p<0.05$). A highly significant difference ($p<0.01$) is marked *

Substances Compared	Day of Experiment	Symptom	χ^2
Hyoscine / Dummy	1 / Control†	Total affected	7·529*
Promethazine / Dummy	1 / Control†	Total affected	5·785
Promethazine / Dummy	1 / Control†	Drowsiness	4·484
Promethazine / ,,	1 / 4	Total affected	4·235
,, / ,,	1 / 4	Drowsiness	4·484

† See text.

Both drugs caused symptoms in a significantly greater number of subjects than the dummy. Drowsiness was about equally frequent after both drugs, but the difference between hyoscine and the dummy was not significant ($\chi^2=3.220$; $p>0.05$). Other symptoms were again more frequent after hyoscine, and this is especially evident if all results obtained during the experiment are considered. Taking the nine symptoms given in Table V, the total number of possible symptoms in four days and with 17 subjects was 612. The number of symptoms recorded after hyoscine was 147, while the number recorded after promethazine was 56, and the difference was significant ($\chi^2=4.835$; $p<0.05$).

Further analysis of the results shows that there was a decline of all symptoms (apart from blurred vision when taking hyoscine) during continued treatment with either drug. With promethazine both the total number affected and the incidence of drowsiness decreased significantly between the first and fourth day of treatment (Table VI), but if all symptoms are taken into consideration this becomes evident for hyoscine also. One hundred and fifty-three symptoms were possible on one day. Fifty-one symptoms were recorded on the first day of taking hyoscine and 25 on the fourth, the difference being highly significant ($\chi^2=10.942$; $p<0.01$). The figures for promethazine were 25 and 8 respectively, and the difference was again highly significant ($\chi^2=8.696$; $p<0.01$). Table V shows that this decrease was gradual and therefore probably caused by habituation, not by a reduction of dosage after the first day of treatment.

Discussion

It can be concluded that hyoscine hydrobromide, promethazine hydrochloride, and diphenhydramine hydrochloride all caused drowsiness and fatigue in a significant number of subjects, while other symptoms were proportionate to the effectiveness of these drugs against seasickness (cf. Glaser and Hervey, 1951). This supports the view that the essential action of antihistamine substances on motion sickness is determined by their hyoscine-like properties, and that side-effects may be inevitable if powerful medication is required (Burn, 1950). It was confirmed that diphenhydramine has a very short action (Landau, Marriott, and Gay, 1948), while promethazine remains effective for a long time (Bain, Broadbent and Warin, 1949). It can be concluded also that fears of cumulative poisoning by hyoscine or promethazine in the present dosage are unfounded and that some tolerance to both hyoscine and promethazine may be acquired within a few days.

Psychological responses were undoubtedly produced by the experimental conditions, but these responses could not have invalidated the results because the experiments were designed to minimize all accidental influences. The evidence of such responses, however, is of great fundamental interest. Symptoms were about equally frequent on the first day of both experiments, whether dummies were given or not, while the giving of drugs and dummies apparently reduced the incidence of effects ; it seems safe to conclude that some symptoms were present because the subjects were asked to look out for them, not because substances had been given. The finding that symptoms gradually decreased not only when drugs were being taken continuously but also when single doses of different substances were given at seven-day intervals suggests that the interest in the experiment must have stimulated certain responses, and this is borne out by the observation that symptoms increased on the last day of the experiment if drugs were given on that day. All this shows a marked similarity with the results of a previous investigation (Glaser and Hervey, 1952) in which 100 men were given varying medications in a random sequence and exposed to identical wave motion six times at 48-hour intervals, and in which there was also a decline of subjective and objective symptoms of seasickness throughout the experiment, followed by an increase on the last day. (In that investigation, as in the present one, the subjects knew nothing about the experimental design, but expected to be told about it after the last test.) The conclusions appear justified that (1) results obtained from human subjects in single tests are liable to fundamental errors, regardless of the number of subjects involved, (2) responses can vary according to the subjects' interest in the experiment, and (3) the processes of adaptation to widely different stimuli, such as taking drugs, exposure to wave motion, or mere participation in an experiment, display certain common characteristics.

It may be queried whether the present findings could be peculiar to Asian races or tropical climates. Racial peculiarities can be excluded, however, since the students belonged to several races, while the Service men and women were all British. A psychological study (Carpenter, 1949), moreover, provides no evidence that the climate of Singapore was conducive to such symptoms as drowsiness and fatigue, though occasional laziness and loss of memory were noted. Finally, dryness

of the mouth resulting from chronic dehydration is unlikely in the climate of Singapore, which is humid and not very hot.

Summary

1. The side-actions of *l*-hyoscine hydrobromide, promethazine hydrochloride, and diphenhydramine hydrochloride were studied in experiments designed to give quantitative data that could be objectively analysed.

2. The results suggest that the side-effects of these drugs are proportionate to their preventive action against motion sickness.

3. The results are compatible with the view that motion sickness remedies have a common hyoscine-like action.

4. Some tolerance to the side-effects of hyoscine and promethazine was acquired when these drugs were given repeatedly for four days.

5. Evidence was found that experimental procedures by themselves can give rise to responses in human experimental subjects and that habituation to diverse experimental procedures may follow a common pattern.

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